

NARRATIVE REVIEW



Traumatic brain injury management in the intensive care unit: standard of care and knowledge gaps

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Abstract

Despite advances in the management of traumatic brain injury (TBI) in the intensive care unit (ICU), and the implementation of new diagnostic techniques and monitoring modalities, the rate of poor neurological outcomes remains high. Specialized neurocritical care units have been shown to improve outcomes. Guidelines have been developed, but most recommendations are based on low levels of evidence. This has led to substantial heterogeneity in clinical practice for many aspects of TBI management, including multimodal neuromonitoring indications, treatment of intra- and extra-cranial complications, and use of prognostic tools. New tools have recently emerged, such as biomarkers and the use of artificial intelligence, but further research is needed to establish their application in clinical practice. This narrative review aims to describe standards of practice for the management of TBI in the ICU, highlighting current evidence and knowledge gaps, to provide a pragmatic approach for clinicians caring for this population.

Keywords: Traumatic brain injury, Outcomes, Intensive care medicine, Secondary brain injury, Biomarkers

Introduction and epidemiology

Traumatic brain injury (TBI) is one of the leading causes of disability and death globally and represents a significant public health burden [1]. The epidemiology of TBI varies by region. Low- and middle-income countries (LMICs) experience a higher burden due to increased rates of road traffic injuries [2]. In contrast, in high-income countries (HICs), falls among elderly individuals, who often have multiple comorbidities, now represent the most common cause.

Managing TBI in the intensive care unit (ICU) is complex. The primary focus is to prevent or mitigate secondary brain injury while accounting for the spectrum of clinical

and pathophysiological heterogeneity of the disease, as well as managing brain-body interactions that may exacerbate the injury. This comprehensive review outlines the current standard of care for severe adult TBI in the ICU, covering guideline-directed initial resuscitation, strategies to reduce secondary insults, and the latest advancements in neuromonitoring techniques. Additionally, we delineate general ICU management practices, the recognition and treatment of extracranial complications, and the use of prognostic tools to assess long-term outcomes.

Pathophysiology of primary and secondary brain injury

TBI comprises a continuum of pathophysiological events that begin with an acute biomechanical insult and evolve into prolonged secondary cascades that critically impact long-term outcomes. Given the heterogeneity of mechanisms underlying the initial impact, including variations in acceleration forces, impact location, and injury type (e.g. closed versus penetrating), TBI is best regarded as a spectrum of conditions rather than as a single entity

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[2]. Moreover, patient-specific factors such as age, sex, genetic background, and comorbidities further modulate injury evolution, although evidence to guide tailored treatment strategies accounting for these variables remains limited. Variants of primary injury, which often coexist, can be divided into focal and diffuse pathology, although it is worth noting that isolated focal injuries are rare [3]. TBI frequently leads to axonal injury, where shear-tensile forces disrupt the axonal cytoskeleton, impair transport, and trigger progressive white matter degradation, even when early imaging appears unremarkable. The biomechanical damage triggers secondary processes, including excitotoxicity, intracellular calcium overload, and dysregulated inflammatory cascades characterized by cytokine release, endothelial, microglial, astrocytic activation, and systemic immune cell activation [4, 5]. In addition, disturbances in lipid metabolism [6] and the microbiome [7] may further promote injury progression. Over time, sustained blood–brain barrier dysfunction, persistent neuroinflammation, and protein misfolding, (e.g. amyloid- β accumulation and tau, TDP43 pathology), contribute to chronic neuronal loss, progressive neurodegeneration, and/or dementia [8]. Simultaneously, the injury induces neurorestorative mechanisms such as neurogenesis, axonal sprouting, and synaptic plasticity, although these endogenous repair processes are typically short-lived and insufficient to counteract injury progression. Clinically, these insights underscore a critical need to develop and implement both early neuroprotective interventions as well as delayed therapies that modulate inflammation and promote neural repair. This complexity challenges clinicians to integrate advanced neuroimaging, blood biomarkers, and genomic profiling toward reclassifying TBI into distinct subtypes defined by specific cellular, structural, and secretomic changes, thereby enhancing individualized management and clinical decision-making in the ICU setting [9].

Early management

In the early phase of TBI, hypoxia, hypotension, and metabolic derangements, individually and in combination, are key secondary insults as they promote cerebral oedema and impact cerebral perfusion and oxygen delivery [10–12].

Guidelines recommend early endotracheal intubation and mechanical ventilation in TBI patients with reduced consciousness (i.e., Glasgow Coma Scale, [GCS] < 9), severe agitation, loss of airway protective reflexes, or a GCS > 8 in the presence of thoracic and abdominal injuries.

Maintenance of peripheral oxygen saturation > 94% or partial pressure of oxygen level between 80 and 120 mmHg is warranted, tempered by growing evidence

Take-home messages

Advances in understanding the pathophysiology of TBI have demonstrated that aggressive detection and treatment of secondary brain insults may improve outcomes.

Current guidelines are generally not based on high levels of evidence, causing wide heterogeneity in monitoring and treatment practices worldwide.

There is a need for more consideration of lower resource settings to improve situationally relevant methods of implementing and delivering treatment.

suggesting that hyperoxemia may be harmful [13, 14]. It is critical to avoid hypercapnic cerebral vasodilation and increased cerebral blood volume (CBV) causing intracranial hypertension as well as hypocapnia with reduced cerebral blood flow (CBF) and potential ischemia. Maintaining a partial pressure of carbon dioxide (PaCO₂) between 35 and 45 mmHg is generally recommended, supporting the use of continuous end-tidal CO₂ measurement.

Hypotension (operationally, but somewhat arbitrarily defined as < 90 mmHg) correlates strongly with poor neurological outcomes [15]. These findings provide a strong rationale for providing appropriate cerebral perfusion pressure (CPP), defined as mean arterial pressure–intracranial pressure). A CPP of 60–70 mmHg is by the latest Brain Trauma Foundation (BTF) Guidelines [16]; however, recent advances suggest that an individualized approach based on patients' autoregulatory status may be useful. There is strong interest in the concept of targeting an optimal CPP (CPP_{opt}), based on optimizing the relationship between CPP and cerebral autoregulation, although rigorous evidence of its efficacy is lacking [17].

Recommendations suggest age-based systolic pressure targets of at least ≥ 100 mmHg or mean arterial pressure > 80 mmHg. Systolic pressure ≥ 110 mmHg might be beneficial, particularly in the elderly [18]. Fluid therapy should be targeted to optimise resuscitation while avoiding volume overload. Vasopressors may be used to assist in achieving hemodynamic targets. Isotonic crystalloids should be considered as the first choice for fluid management, as hypertonic saline resuscitation has not shown outcome benefits and hypo-osmolar solutions may exacerbate cerebral oedema [19–21]. Abnormalities in glycemia and temperature represent additional drivers of secondary injury and require meticulous attention during the initial phase. The use of tranexamic acid in isolated TBI has shown no improvement in clinical outcomes [22].

In summary, although randomized controlled trials are lacking, protocolized control of oxygenation, ventilation, hemodynamic status and other physiological variables in

the initial resuscitation phase are consistently associated with improved survival [23].

Basic and advanced neuroimaging for TBI

Computed tomography (CT) has a high sensitivity and specificity for identifying clinically significant intracranial injury and craniofacial fractures. Its advantages over magnetic resonance imaging (MRI) include short imaging acquisition time and fewer potential risks and contraindications. Therefore, CT represents the main imaging modality for initial diagnosis and interval imaging in the acute and subacute phase of TBI.

CT angiography can be considered following trauma to assess for blunt cerebrovascular injuries (BCVIs, including carotid and vertebral artery injury) which can increase the risk of stroke (<https://www.facs.org/media/vgfgjpfk/best-practices-guidelines-traumatic-brain-injury.pdf>). Several studies now recommend universal BCVI screening for all patients with major trauma using a whole-body CT, with the highest yield in patients with skull or spine fractures, TBI with thoracic injuries, or neurological exam findings not explained by neuroimaging (<https://www.facs.org/media/vgfgjpfk/best-practices-guidelines-traumatic-brain-injury.pdf>).

Conventional MRI provides a more refined characterization of the distribution and extent of injury than CT; both within specific neuroanatomic locations (e.g., brainstem injury) and for the detection of lesion types (e.g. cerebral microhaemorrhages) [24]. Currently, MRI is most commonly used for the evaluation of specific clinical concerns, e.g. unexplained focal neurologic deficits and in patients with prolonged disorders of consciousness (coma) to investigate for lesions not detected by CT and assist in prognostication (Fig. 1).

Quantitative MRI techniques may detect damage otherwise not visible and offer unique pathophysiological insights. These include volumetric analysis, variants of diffusion MRI (dMRI, most commonly diffusion tensor imaging), quantitative susceptibility mapping, MRI perfusion imaging (e.g. dynamic contrast-enhanced MR perfusion) and resting state functional MRI [24–26]. Of these, the most studied modality in the acute phase is dMRI which characterises the diffusion of water molecules. This diffusion may be influenced by tissue microstructure which changes after injury, therefore, offering pathological insights. For example, in the hyperacute phase, contusions may have areas of both vasogenic oedema (unrestricted diffusion) and cytotoxic oedema (restricted diffusion) [25]. Cytotoxic oedema may represent microvascular injury, which could provide a target for future therapeutic trials [27] (Fig. 1). Diffusion tensor imaging (DTI) metrics are of particular importance as they may guide the prediction of emergence

from a coma and hold promise for neuroprognostication [28, 29]. Improvements in sequence harmonisation, automatic quantification of brain injury, and a better understanding of individual results are needed before widespread implementation into clinical practice.

Brain-targeted monitoring and management

Intracranial pressure monitoring indications and management

Measurement of intracranial pressure (ICP) and derived parameters after TBI remain a subject of intense focus and investigation [30]. Though evidence indisputably supporting the benefit of current therapy based on ICP monitoring is lacking, such monitoring is generally viewed as fundamental to modern brain injury care [16]. Indeed, ICP monitoring is required for American College of Surgeons trauma center accreditation in the United States.

ICP measurement provides more than a threshold to be maintained via titration of therapeutics—it can detect expanding intracranial mass lesions and inform ICP dose, cerebral perfusion pressure, optimal cerebral perfusion pressure, autoregulatory status, and compliance/compensatory reserve [31].

The BTF Guidelines recommend that ICP monitoring be used in the context of (1) coma and an abnormal head CT [16, 32, 33] and (2) comatose patients with a normal head CT exams but two or more of the following characteristics: age over 40, hypotension, or posturing on neurologic examination [34]. Evidentiary support for these indications did not meet the criteria for inclusion in the most recent 4th edition of the BTF adult guidelines [16]. However, the authors chose to reiterate these recommendations within the guidelines to maintain sufficient recognition of patient characteristics associated with a risk of increased intracranial pressure.

A consensus conference held in Milan in 2013 concluded that a more conservative approach to ICP monitoring was warranted [35], recommending monitoring in comatose TBI patients with cerebral contusions where the interruption of sedation to check neurological status is considered dangerous or the clinical examination is not reliable, or following a secondary decompressive craniectomy to assess the effectiveness of ICP control and guide further therapy. The consensus group did not recommend ICP monitoring in comatose TBI patients where the CT scan was normal. The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) revisited indications for ICP monitoring using an established, rigorous Delphi consensus process [36]. The results demonstrated that the author group would use ICP monitoring more liberally than either the BTF

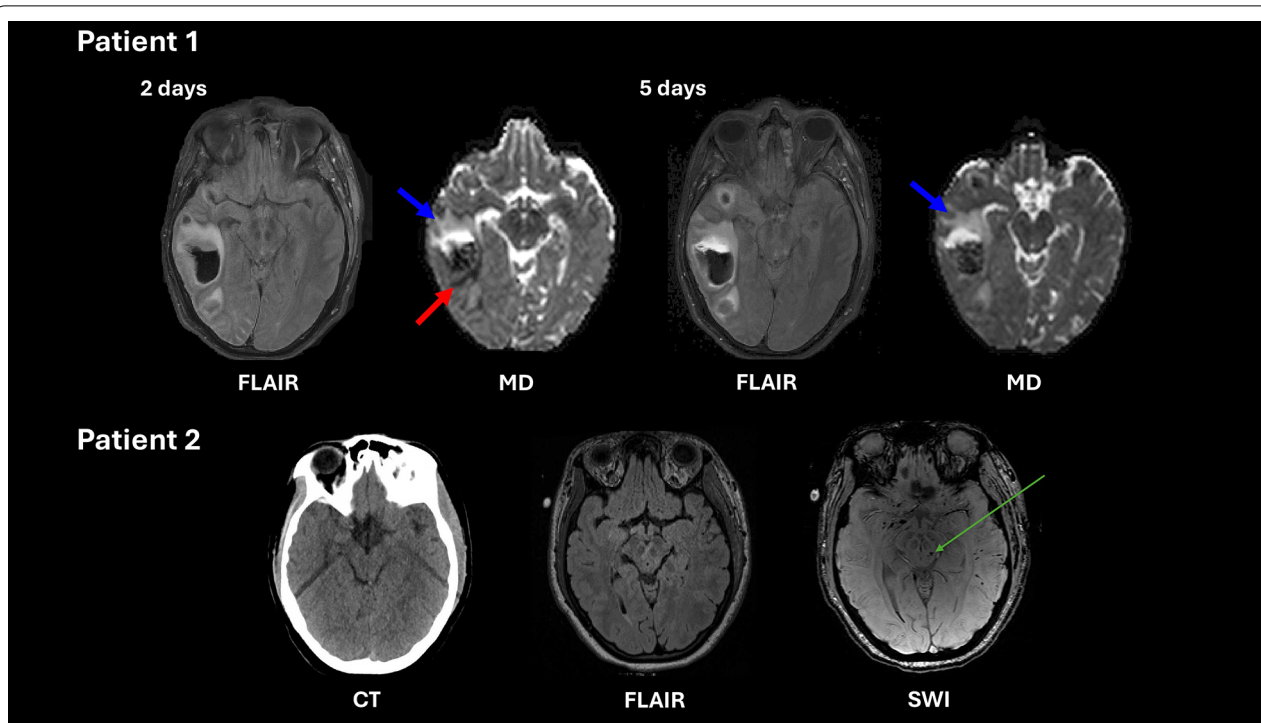


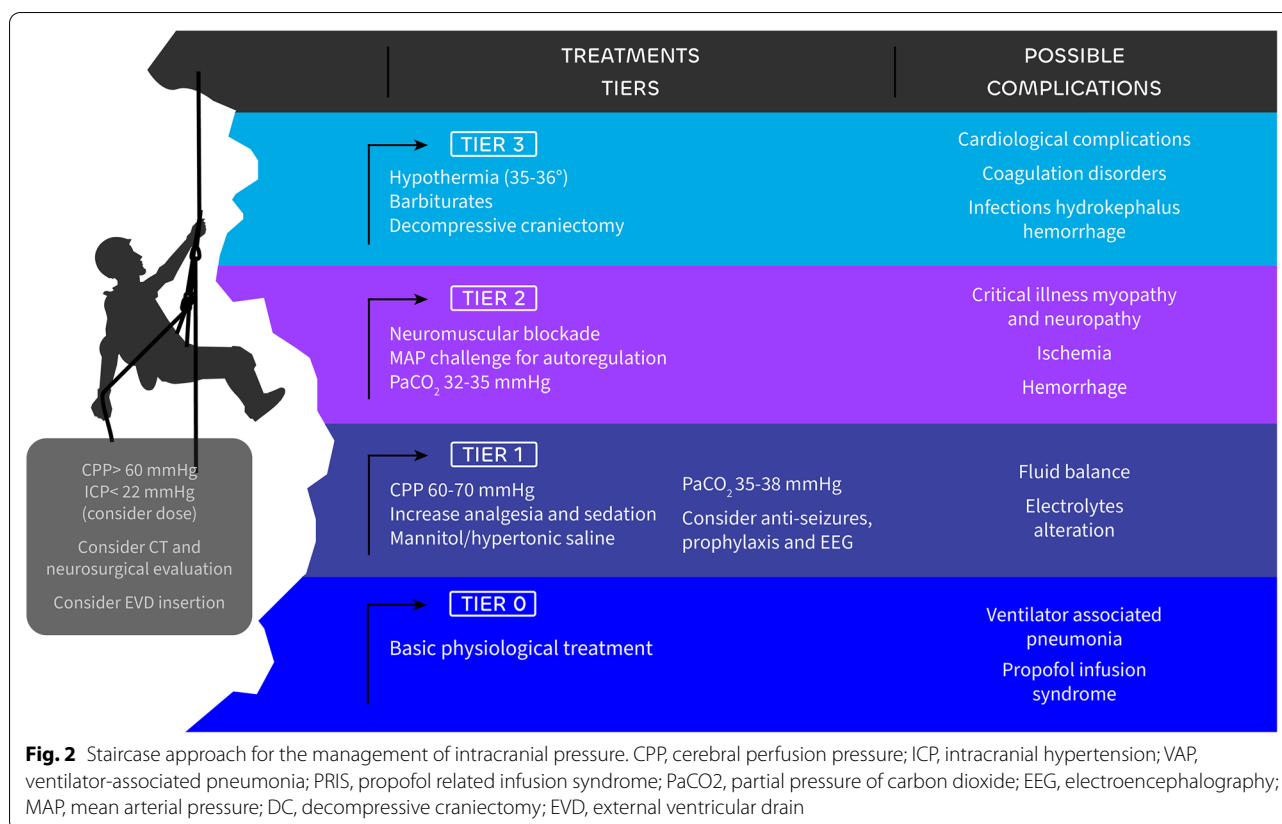
Fig. 1 Images demonstrating the potential value of MRI in the acute phase of TBI. Patient 1 was imaged on day 2 and 5 after sustaining a TBI. The mean diffusion map illustrates how different types of oedema may be distinguished, with the blue arrow pointing to vasogenic oedema (unrestricted diffusion) surrounding a contusion with the red arrow pointing to a small rim of cytotoxic oedema (restricted diffusion). By day 5, the cytotoxic area is no longer visible. This area of hypointensity around contusions in the hyper-acute phase may represent an area of microvascular failure. Patient 2 has diffuse axonal injury and underwent MRI on day 3 after injury. Petechial haemorrhages can be seen on the susceptibility-weighted imaging (SWI) in the left dorsal midbrain and bilateral temporal lobes. These lesions are not visible on the FLAIR or CT scan. Newcombe et al. [27]. FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; TBI, traumatic brain injury; MD, mean diffusivity

or Milan recommendations and that they value ICP data beyond simply detecting and monitoring severe intracranial hypertension. Given this, recent advances in predicting intracranial pressure elevation [37] may not be sufficient for developing future recommendations related to indications for intracranial pressure monitoring. Though reasonably well described, the phenomenon of ICP elevation, when cranial imaging is normal [34] merits further study.

Numerous treatments for ICP elevation have been devised [38]. Treatment protocols have advocated for using treatments with less risk with gradual escalation to those with more substantial risk. Contemporary protocols have organized these treatments into three tiers based on risk: benefit ratio [39, 40] as opposed to the preceding “stair-case” approach which prescribed a specific sequence of individual treatments, with aggressive treatments (decompressive craniectomy, hypothermia, barbiturates) reserved only for cases of refractory intracranial hypertension (Fig. 2).

Advanced invasive neuromonitoring

Beyond ICP monitoring, several invasive techniques have been proposed to assess cerebral oxygenation and metabolism, including brain tissue oxygen monitoring (PbtO₂) and cerebral microdialysis. PbtO₂ monitoring is increasingly used to detect brain hypoxia in severe TBI, [41] since low PbtO₂ levels have been associated with poor neurological outcome [42] independently of ICP/CPP measurements [43] (Fig. 3). A Phase II prospective randomized controlled trial (BOOST II) investigating PbtO₂-guided management of severe TBI compared treatment based solely on ICP monitoring with treatment guided by both ICP and PbtO₂ [44]. The study showed that the ICP + PbtO₂ group had a statistically significant reduction in the duration and severity of brain hypoxia. Although it was a feasibility trial and not powered to detect significant differences in overall outcomes, it did reveal a trend toward lower mortality and improved neurological recovery at 6 months. The Oxy-TC randomized trial found no significant difference in functional outcomes between blunt TBI patients treated with ICP + PbtO₂ monitoring versus those managed with ICP



monitoring alone [45], despite a signal of benefit observed in the subgroup with increased ICP. Other, larger Phase III trials (BONANZA: ACTRN12619001328167 BOOST III: NCT03754114) are currently underway to compare outcomes between ICP-only management and ICP + PbtO₂-guided therapy [46].

CMD has enhanced understanding of acute brain dysfunction after TBI and may serve as an additional bedside neuromonitoring tool [47]. An abnormal lactate/pyruvate ratio, defined as >25, is associated with poor TBI outcomes, with values >40 indicating a cellular energy crisis. In practice, values above 35–40 often trigger therapeutic interventions [48]. However, being resource-intensive and lacking strong evidence of clinical efficacy, cerebral microdialysis has not been implemented in neuro-ICUs worldwide.

Non-invasive neuromonitoring

Current non-invasive neuromonitoring tools that are commercially available for clinical utilization include pupillometry, brain ultrasound, and electroencephalography [49].

Current paradigms for pupillometry use dedicated devices to quantitatively assess pupillary light reaction. This provides a more accurate analysis of pupillary

function than standard subjective evaluation [50, 51]. All devices evaluate pupillary light response to derive consistent measurements of latency and amplitude and velocity of pupillary constriction and dilation. Some devices have proprietary indices that may predict neurological decline and prognosis [52]. The role of pupillometry in assessing ICP is still debated [49].

Ultrasound-based assessment of cerebral perfusion has been used noninvasively for decades for neuromonitoring. Quantitative cerebral blood flow velocity derived from transcranial Doppler (TCD) can be used to calculate ICP and was the subject of investigation in the IMPRES-SIT-2 trial which found it useful to rule out high ICP [53]. An index of cerebrovascular resistance calculated using TCD (called the pulsatility index) and its derivatives can also be used in non-compartmentalized cerebral oedema such as occurs in TBI [54]. Assessments of optic nerve sheath diameter (ONSD) have also been recently widely investigated and represent an easily accessible, bedside tool that can serve as a non-invasive surrogate for invasive ICP measurement.

The recent B-ICONIC expert consensus-based guidelines provide a framework for employing noninvasive multimodality monitoring (including pupillometry, ONSD, pulsatility index from TCD measurements as

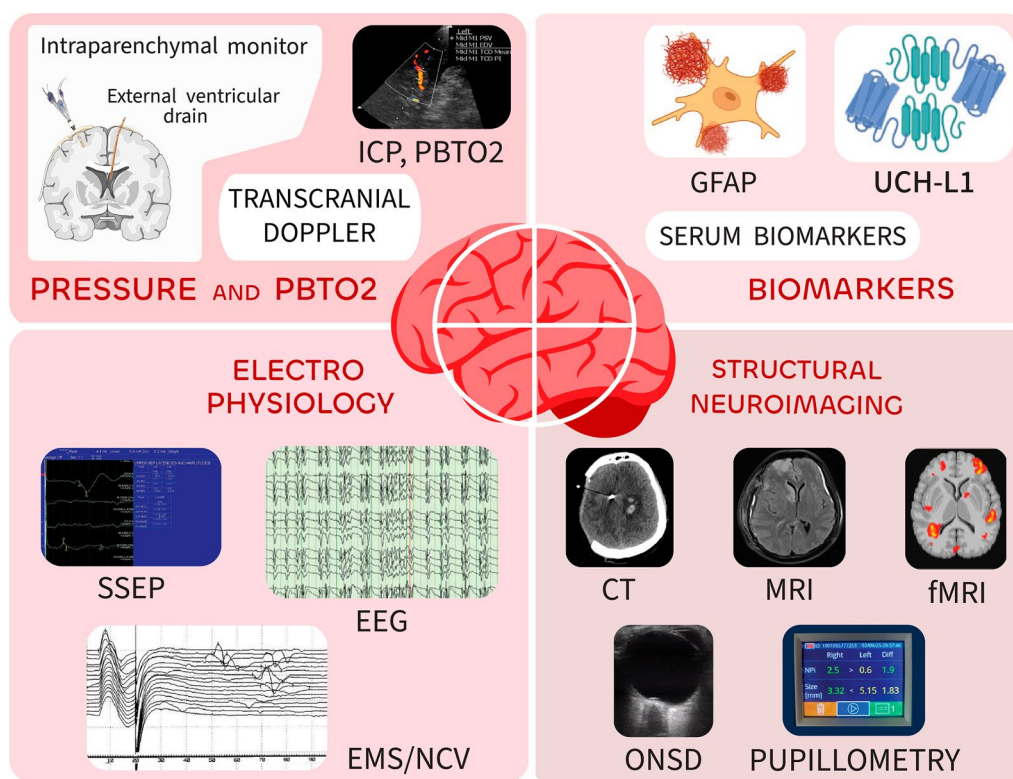


Fig. 3 Invasive and non invasive multimodal neuromonitoring in traumatic brain injury patients. EEG, electroencephalography; SSEP, somatosensory evoked potential; EMS/NCV, electromyography/ nerve conduction velocity; TCD transcranial Doppler; ICP, intracranial pressure; PbtO₂, brain tissue oxygenation; CT, computed tomography; MRI, magnetic resonance imaging; fMRI, functional MRI; ONSD, optic nerve sheath diameter; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin C-terminal hydrolase L1

well as noninvasive ICP calculated using TCD measurements) [49] to assess for intracranial hypertension in low-resource settings. Although these tools cannot fully substitute for invasive ICP, they may be particularly useful under conditions where ICP is not available or contraindicated, or as complimentary to invasive ICP to better understand cerebral physiology.

Electroencephalographic (EEG) techniques have been widely used in the intensive care of TBI [55, 56]. These include a qualitative review of waveforms for seizures, quantitative EEG parameters (amplitude-integrated EEG, the relative band power, the relative alpha variability, the spectral entropy) and EEG reactivity. This can be not just for the evaluation of seizures but also for prognostication, with new evidence supporting the value of using artificial intelligence assisted EEG-models for prognostication [57]. Current evidence is insufficient to recommend the use of continuous vs intermittent EEG, so the decision should be made according to local availability and clinical conditions.

There have been recent promising efforts to use skull- elastometry-based evaluations to measure intracranial pressure and compliance (brain4care, Inc) but these need

further validation before being considered for clinical use [58, 59].

Systemic management

Ventilatory management

There are several unique clinical considerations when managing patients with TBI who require invasive mechanical ventilation [12, 60].

Experimental and clinical studies have described complex, closely intertwined, often bi-directional interactions between cerebral and pulmonary pathophysiology ("brain-lung crosstalk").

Patients with acute brain injury have been historically underrepresented in trials investigating mechanical ventilation practices. A main concern has been the risk of elevated ICP with low tidal volume ventilation, higher levels of post-end-expiratory pressure [61], or prone positioning [62]. This has resulted in potential conflicts in managing TBI and concomitant acute respiratory distress syndrome (ARDS) [63, 64].

While optimal ventilatory targets in acute brain injury are insufficiently explored [65], a growing body of evidence has recently emerged. High tidal volumes have

been associated with poor outcomes in brain-injured patients [66]. The recent PROLABI-RCT compared a lung-protective strategy compared with conventional ventilation in a non-ARDS acute brain-injured population and did not demonstrate differences in mortality, ventilator dependence, or ARDS [67]. However, the implications of this trial are unclear, as the trial was underpowered, terminated early, and did not account for the effects of sedation or neuromuscular blockade to maintain low tidal volume ventilation. Other ventilator parameters that seem to be associated with outcomes in recent large, prospective, multicenter studies of brain-injured patients include mechanical power, driving pressure, peak pressure, and plateau pressure [60, 68, 69]. A recent observational study—VENTIBRAIN—suggested that lung protective ventilation strategies are commonly used in this population and that these are associated with improved mortality [60].

The 2020 European Society of Intensive Care Medicine (ESICM) consensus guidelines on mechanical ventilation in acute brain injury recommend targeting a partial pressure of oxygen of 80–120 mmHg, emphasizing higher values compared to recommendations for general critical care populations (≥ 55 mmHg). Though both hypoxemia and hyperoxemia have been associated with poor outcomes in TBI [70, 71], the exact cutoff values of the U-shaped curve remain to be determined, and targets may have to be individualized.

A powerful mediator of cerebrovascular tone, partial pressure of PaCO_2 can impact ICP and cerebral perfusion. Exposure to hyper- and hypocarbia has been associated with poor outcomes in brain-injured patients [72, 73]. Maintaining PaCO_2 in the physiologic range is recommended. Profound hyperventilation is risky and should be used only as a short-term measure in case of brain herniation [12]. Slightly lower PaCO_2 ranges (32–35 mmHg) are part of the ICP management tiers in TBI and seem to be safe, despite additional neuromonitoring with PbtO_2 being suggested.

The ability to predict successful extubation in patients with impaired airway protective reflexes remains a major challenge [74–77]. ENIO, the largest prospective study of this question to date included 48% of participants with TBI). It showed that extubation failure was less likely in TBI compared to other brain injuries. Factors associated with extubation success and that should be taken into account include vital signs, gag, suctioning frequency, swallowing attempts, visual pursuit, GCS, and prophylactic physical therapy [78]. The most recent Guidelines suggest considering GCS motor score of >6 , normal respiratory drive, stable intracranial conditions, intact airway protective reflexes (vigorous cough, gag reflex, and swallowing attempts), and endotracheal suctioning ≤ 2

times per hour before proceeding with an extubation trial [79].

Tracheostomy practices have been highly variable in brain-injured patients. A prospective CENTER-TBI study described tracheostomy rates of 8–50%, with further practice variations in tracheostomy timing [80]. Late tracheostomy was associated with worse neurologic outcomes. The recent SETPOINT-2 RCT did not demonstrate the benefits of early tracheostomy in a mixed-stroke population [81]. Still, the recent 2024 guidelines from the American College of Surgeons, advised considering early tracheostomy (<7 days) in critically TBI-ill patients.

Management of patients on antithrombotics and thromboprophylaxis

With the shift towards an increasingly elderly TBI population, previous use of antithrombotics due to medical comorbidities has become more prevalent [82]. Immediate reversal of drug-induced therapeutic coagulopathy is essential after TBI. The 2024 ACS Best Practice Guidelines on the Management of Traumatic Brain Injury are the most recent guidelines containing specific recommendations on antithrombotic reversal and restarting and optimal timing of starting thromboprophylaxis (<https://www.facs.org/media/vgfgjpjk/best-practices-guidelines-traumatic-brain-injury.pdf>).

Acute reversal of anticoagulants (vitamin K antagonists, and direct oral anticoagulants) is well established in clinical practice, although the ACS guidelines advise to ‘consider anticoagulant reversal’ rather than dictate it for all patients with TBI. Acute reversal is advised with a high likelihood of bleeding risk, especially for patients requiring emergent surgery, or external ventricular device placement, those considered at high risk for hematoma expansion, and patients with life-threatening bleeding. Hemorrhagic lesions on admission CT have the highest risk of progression in the first 24 h after trauma [83], with a much higher risk in the first minutes to hours after injury, and hematoma progression is strongly associated with worse outcomes, supporting acute anticoagulant reversal.

Reversal of antiplatelet therapy with fresh thrombocytes is less straightforward. Although intuitively indicated with significant cerebral haemorrhage, there is also the risk of harm, as shown for spontaneous intracerebral haemorrhage. Therefore, platelet infusion is not advised in stable (i.e. non-bleeding) and non-(neuro) surgical TBI patients [84] for use in reversing antiplatelet agent effects. Recent guidelines recommend the use of clinical judgment to determine if patients with TBI on antiplatelet agents who are undergoing surgery

or invasive procedures with low platelet counts need platelet transfusions to achieve hemostasis [79].

Restarting anticoagulants is generally based on a risk–benefit assessment and the evaluation of interval CT scans for bleeding progression or stability. Commencing with low molecular weight heparin or heparin is often advised before oral anticoagulation. Restarting can be delayed for many weeks in case of atrial fibrillation [85], although absolute risk for thromboembolic complications due to atrial fibrillation may guide individualized timing of restarting.

There appears to be consensus that pharmaceutical venous thromboembolism prophylaxis should be commenced within 72 h after TBI unless specific concerns exist to withhold it. Strong evidence to guide individualizing earlier or later starts within this timeframe is absent, so guideline recommendations currently vary [85].

Venous thromboembolism prophylaxis is recommended within 24–48 h after injury in patients with moderate- or high-risk nonoperative TBI, provided the follow-up head CT shows no progression of intracranial injury. It is also recommended to begin venous thromboembolism prophylaxis within 24–48 h after craniotomy or craniectomy in patients if intracranial hemorrhage is stable on postoperative CT.

With respect to effective vitamin K antagonist reversal it is not clear if 4-factor prothrombin concentrate should be administered as a fixed dose or using weight-based dosing. For direct oral anticoagulants, laboratory-based assays are ill-defined, hampering precision dosing for pharmaceutical reversal.

Timing of restarting therapeutic anticoagulants and antiplatelet therapy after TBI requires randomized evidence to inform more individualized recommendations. The timing of the start of pharmaceutical thromboprophylaxis within the 72-h timeframe and the relative effectiveness of mechanical versus pharmaceutical thromboprophylaxis also require further evaluation [86–90]. Electronic supplementary material (ESM) Table S1 summarizes the most recent guideline recommendations for antithrombotics' reversal and restart and thromboprophylaxis in TBI.

Fluids, transfusion and hemodynamic management

Hemodynamic management remains a frequent and complex clinical challenge in the care of patients with TBI, due to the presence of concomitant hemorrhagic or spinal shock, the need to optimize cerebral perfusion, or the management of secondary systemic complications such as sepsis or gastrointestinal bleeding [91, 92]. Crystalloids remain the first-line choice for fluid therapy in the ICU, with balanced solutions being associated with

increased 90-day mortality, particularly in patients with a GCS < 6 [93]. Similar results were observed in a secondary analysis of a large randomized trial, after adjustment for several confounders [94].

While avoiding hypovolemia is crucial to maintaining adequate systemic and cerebral perfusion, the risk of fluid overload should not be underestimated. Significant variability in fluid management practices has been observed among patients with TBI, with more positive fluid balances correlating with poorer outcomes [95]. However, the feasibility and clinical benefit of targeting a neutral fluid balance is scientifically debated and diverging opinions currently coexist. The goals are optimizing volume status and cerebral perfusion and oxygenation while minimizing the risks of fluid overload and its associated complications. It is currently uncertain whether using cardiac-output or neuromonitoring methods to direct individualized approaches to hemodynamic and fluid management strategies is useful.

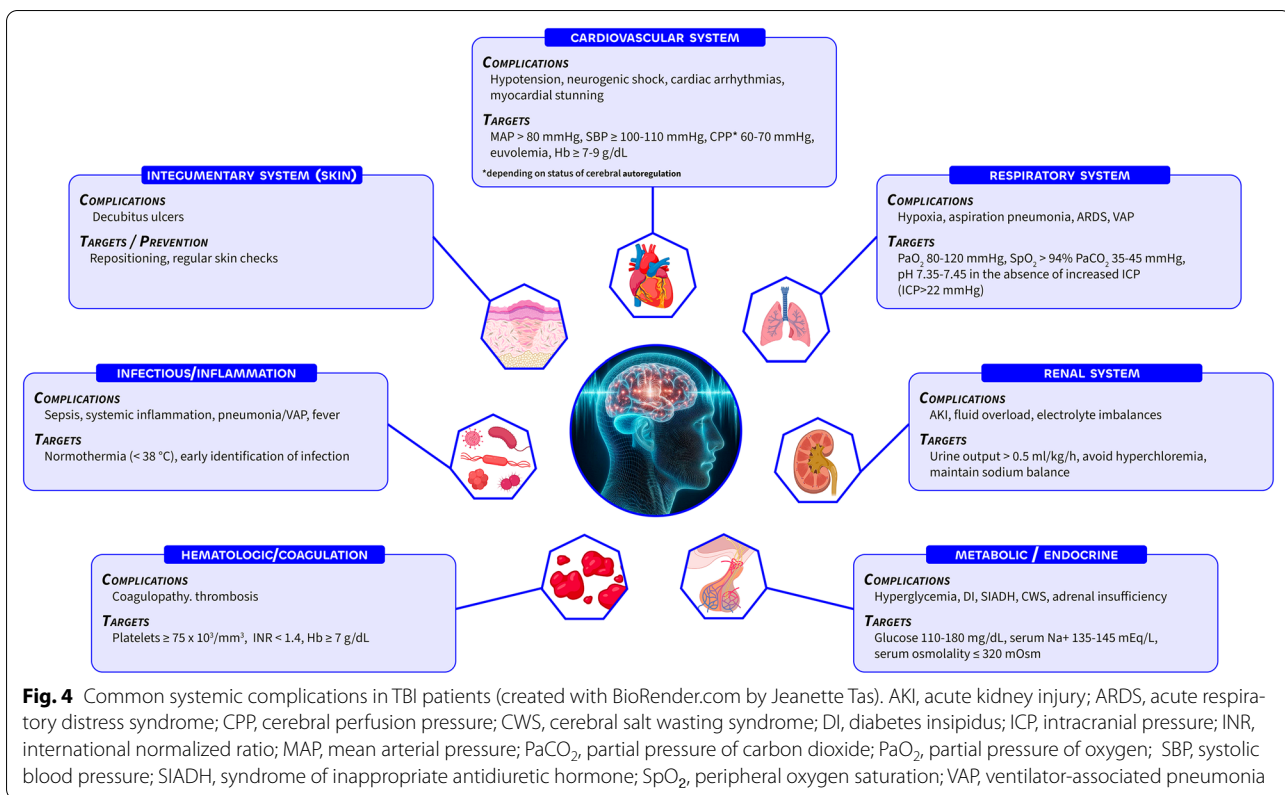
Widespread adoption of vasopressor use to maintain CPP between 60 and 70 mmHg has the potential to prevent hypotension, partially compensate for hypovolaemia and avoid fluid overload. Although there are presently no specific indications as to the type and role of advanced hemodynamic monitoring, this should be considered in hemodynamically unstable patients, or those who require high doses of inotropes or vasopressors.

Two recent randomized controlled trials have evaluated liberal (<9–10 g/dL) versus restrictive (<7 g/dL) haemoglobin transfusion threshold strategies in TBI patients. One study reported a non-significant 6% absolute reduction in unfavourable neurological outcomes at 6 months with the liberal strategy [96]. The other trial demonstrated a significant 10% absolute reduction in unfavourable neurological outcomes associated with higher haemoglobin targets in a mixed population of acute brain-injured patients, with consistent benefits observed in the TBI subgroup [97]. These findings suggest that higher haemoglobin thresholds for red blood cell transfusion may be warranted in this patient population.

Other (acute kidney injury, electrolyte dysfunction, nutrition)

Among the common complications associated with TBI and its acute management, seizures, acute kidney injury, and electrolyte disturbances are particularly notable (Fig. 4).

Seizures are a frequent and debilitating complication after TBI, affecting approximately 20–50% of patients depending on the severity and location of the injury. Seizures can be categorized into early and late seizures based on the timing of occurrence (<7 days versus >7 days after injury). Early post-traumatic seizures occur in



50% within 24 h and are more common in children (30–35% versus 10–15% in adults) and in patients with a history of penetrating brain injuries, cortical contusions, or subdural hematomas [98]. These factors increase the risk of late seizures, which can have a considerable latency period but usually start within 2 years of the injury (80%).

The BTF guidelines recommend the use of phenytoin to decrease early post-traumatic seizures (Level IIA) after weighing the benefits over treatment-associated risks of such treatment [33]. Importantly, early antiseizure medication does not prevent late-onset seizures or post-traumatic epilepsy and does not improve functional outcomes [99]. Prophylactic antiepileptic therapy should only be used for a short time after TBI as they may have adverse effects on neurocognitive recovery (esp. phenytoin). For patients with early post-traumatic seizures, antiepileptic drugs should be started promptly and continued for a few weeks. Besides benzodiazepines (lorazepam, diazepam), fosphenytoin, sodium valproate, and levetiracetam are the drugs of choice and are usually effective [100].

Acute kidney injury affects up to 17% of TBI patients, most commonly occurring within 5 days (>90%) after trauma and is associated with higher mortality [101]. Etiologic factors include hypotension and hemodynamic instability, neurohumoral changes, rhabdomyolysis,

direct effects of the trauma, or medication-associated nephrotoxicity [102]. Acute kidney injury is more common in male patients and those with severe TBI. Early management strategies include preservation of renal perfusion through immediate fluid resuscitation, and correction of electrolyte imbalances, which is particularly important in hypotensive and hemodynamically unstable patients. In more severe cases, renal replacement therapy may be required, although the indications are not well defined and evidence does not support an effect on TBI outcome. Careful monitoring of serum urea and sodium is needed to prevent brain oedema. Therefore, continuous renal replacement therapy is usually preferred over intermittent haemodialysis, especially in hemodynamically unstable patients and those with a high risk of raised ICP.

TBI-associated electrolyte disturbances occur in up to 2/3rds of TBI patients and include alterations in sodium, potassium, magnesium, and calcium [103]. Sodium abnormalities are most common and result from damage to the hypothalamus, pituitary gland or other areas regulating fluid and electrolyte balance and also from renal/adrenal insufficiency. Hyponatremia can lead to cerebral oedema, worsening of ICP, and a negative impact on brain recovery. Clinical manifestations of dysnatremia include diabetes insipidus (DI), cerebral salt wasting

(CSW), and the syndrome of inappropriate antidiuretic hormone (SIADH) (Fig. 4). DI is usually transient after TBI and associated with decreased antidiuretic hormone secretion, which produces decreased water reabsorption, resulting in hypotonic polyuria, dehydration and hyponatremia. SIADH results in excessive ADH secretion, causing water retention and hyponatremia. In contrast, CSW leads to hypovolemic hyponatremia through renal loss of sodium and water. All conditions can occur concurrently after TBI and require careful monitoring of electrolyte levels and fluid balance with disorder-specific therapies, such as fluid replacement (mild DI) additional hormonal replacement (severe DI), higher volume normal saline infusions (SIADH) or volume replacement with sodium-containing fluid (CWS).

Calcium and magnesium imbalances are significant disorders as well related to their crucial roles in cellular function and neuronal excitability. Hypocalcemia and hypomagnesemia have been associated with increased risks of seizures and require careful supplementation.

Recent guidelines suggest initiating enteral nutrition support once a patient is hemodynamically stable, ideally within 24–72 h of injury, with the aim of achieving full nutritional supplementation within 7 days of injury. Post-pyloric feeding access is generally preferred. However, when obtaining this access causes a delay in enteral nutritional support, early initiation via gastric access is acceptable. Parenteral nutrition support is recommended only when enteral nutrition is contraindicated [79].

Prognostication

Prognostication is essential for determining treatment intensity, guiding rehabilitation strategies, and informing decisions regarding withdrawal of life-sustaining treatment. However, predicting functional recovery or mortality remains imprecise, with substantial uncertainty even when using established prognostic tools [2, 104]. Research indicates that withdrawal of care is the primary cause of death in TBI patients in the ICU, often occurring within the first 2 weeks post-injury. This highlights the critical importance of careful prognostication [105].

Several clinical factors such as GCS score [106], pupillary reactivity, and age have been associated with outcomes in TBI, although their reliability is variable. Individual predictors alone are insufficient for precise prognostication, leading to the development of predictive models integrating multiple variables, such as the Corticosteroid Randomization After Significant Head Injury (CRASH) and the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) models [107]. Although these models enhance predictive accuracy, they remain only moderately reliable, and

their use must be contextualized within a broader clinical framework.

Given these complexities, prognostication should be multimodal, incorporating serial clinical assessments, neuroimaging, and electrophysiological studies where appropriate [108]. Functional magnetic resonance imaging and electroencephalography may help to better understand the pathophysiology of disorders of consciousness [109] and aid in prognostication.

Clinicians must acknowledge the inherent uncertainty in all predictive models and communicate prognostic estimates transparently to surrogate decision-makers, emphasizing that outcomes exist along a spectrum rather than within binary categories. Ethical considerations necessitate shared decision-making that respects patient values and minimizes the risk of premature treatment withdrawal. Future research should focus on refining prognostic models by integrating biomarkers, such as glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) [110], advanced imaging techniques, and machine learning approaches to improve individualized outcome prediction.

TBI management in low-income countries: any difference?

Although TBI is physiologically similar globally, what is considered optimal management is difficult to achieve in many environments and the literature is largely driven by studies performed in HICs despite the greater burden of disease in LMICS.

HICs' dominance of the literature deceptively sets non-generalisable standards. Varying environmental-specific priorities interact with widespread resource and monetary limitations to confound the adoption of many HIC-generated solutions.

Situationally specific approaches are necessary [49].

Recent research has demonstrated 6-month results in LMICs comparable with HICs despite limited resources [111]. Prospective testing has demonstrated that protocolisation is associated with improved outcomes and that the CREVICE protocol, a consensus-based protocol based on clinical picture and neuroimaging without ICP monitoring, is safe and effective [112–114]. Providing a “TBI-management-algorithm toolbox” adaptable to local reality is a realistic option [115]. ICU bed insufficiency severely limits care delivery, denying many patients ICU-based care. The efficacy of the common practice of using decompressive craniectomy as a proxy for non-surgical resource limitations requires investigation. Economical, reusable non-invasive ICP monitoring technology could strongly improve care quality and efficiency.

Unfortunately, excellent ICU care includes pre- and post-hospital support. Minimal availability of medical

transportation interacts with issues of distance and traffic congestion to prevent early interventions against secondary brain insults, influencing salvageability and pre-hospital survival selection. Innovative use of available resources (such as using taxi drivers as first responders [116] and hierarchical TBI resuscitation networks) might mitigate such barriers pending larger-scale solutions. Rigorous transportation, resuscitation, and arrival data are required.

Post-discharge rehabilitation is essentially absent in terms of availability and affordability. Acute-care-driven recovery potential is thereby blunted. Creative temporizing approaches such as using nuclear-family resources to deliver therapies should be studied. Acquiring prospective long-term follow-up data is critical.

Understanding and balancing the multifactorial needs of TBI management against currently available resources requires multidisciplinary collaboration, coupled with administrative recognition of the magnitude of the problem. Conceptual (e.g. physiologic) “solutions” from HIC literature must be integrated with situational awareness to guide the provision of effective care. The misleading amalgamation of all resource-limited realities under the LMIC designation must be replaced by a more pragmatic conceptualization.

The future of TBI management: AI, genetics, biomarkers

For decades, the dominant approach to managing TBI has been to treat it as an acute event. Severe cases are identified based on the patient’s level of consciousness and CT findings and require a set of interventions during this acute phase to prevent or mitigate secondary brain injury, typically guided by uniform thresholds for ICP and CPP. Historically, there has been no targeted intervention for less severe TBI, and no universally accepted treatment during the post-acute phase of severe TBI. Unfortunately, once this phase has passed, the outcome has been considered irreversible.

Biomarker and advanced imaging studies have taught us that TBI is not a single pathological entity [117] (Fig. 5), but can be stratified based on its radiological and biomarker profile. This allows the potential to develop more personalized treatment strategies, allowing targeted interventions based on a patient’s specific injury profile. Brain injury biomarkers such as glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), and S100 calcium-binding protein (S100B) can be used to rule out the need for brain CT imaging for patients with suspected TBI with GCS of 13–15. The extent of GFAP, UCH-L1, and S100B elevation on the day of injury provides clinicians with an estimate of the underlying structural brain injury severity. These blood levels are also useful as adjuncts for predicting functional

recovery at 6 months postinjury in patients with GCS 3–12 associated with TBI [79].

Neuroinflammation and secondary brain injury have been shown to continue to be active months and years beyond the acute phase [118, 119], so targeting neuroinflammatory pathways and oxidative stress could mitigate secondary damage and improve outcomes. Acting on multiple repair mechanisms, mesenchymal stromal cell-based therapy, holds potential in the recovery phase of anatomical damage, with beneficial effects on cognitive and sensorimotor function [120], and some neuromodulatory therapies having shown promising results [121].

Artificial intelligence(AI)-driven decision support has the potential to revolutionize patient management in neurocritical care [122], even while currently most applications are stuck at low technology readiness levels [123]. Already, AI is being used for neuroimaging- and EEG-interpretation, improving workflow efficiency, and enabling real-time seizure detection, although its role is assistive rather than replacing clinicians. In decision support, predictive models using multimodal neuromonitoring data offer not only the potential to personalize secondary brain injury definitions but also to predict them such that they may be proactively prevented, requiring a shift in clinical practice towards probability-based interventions [124].

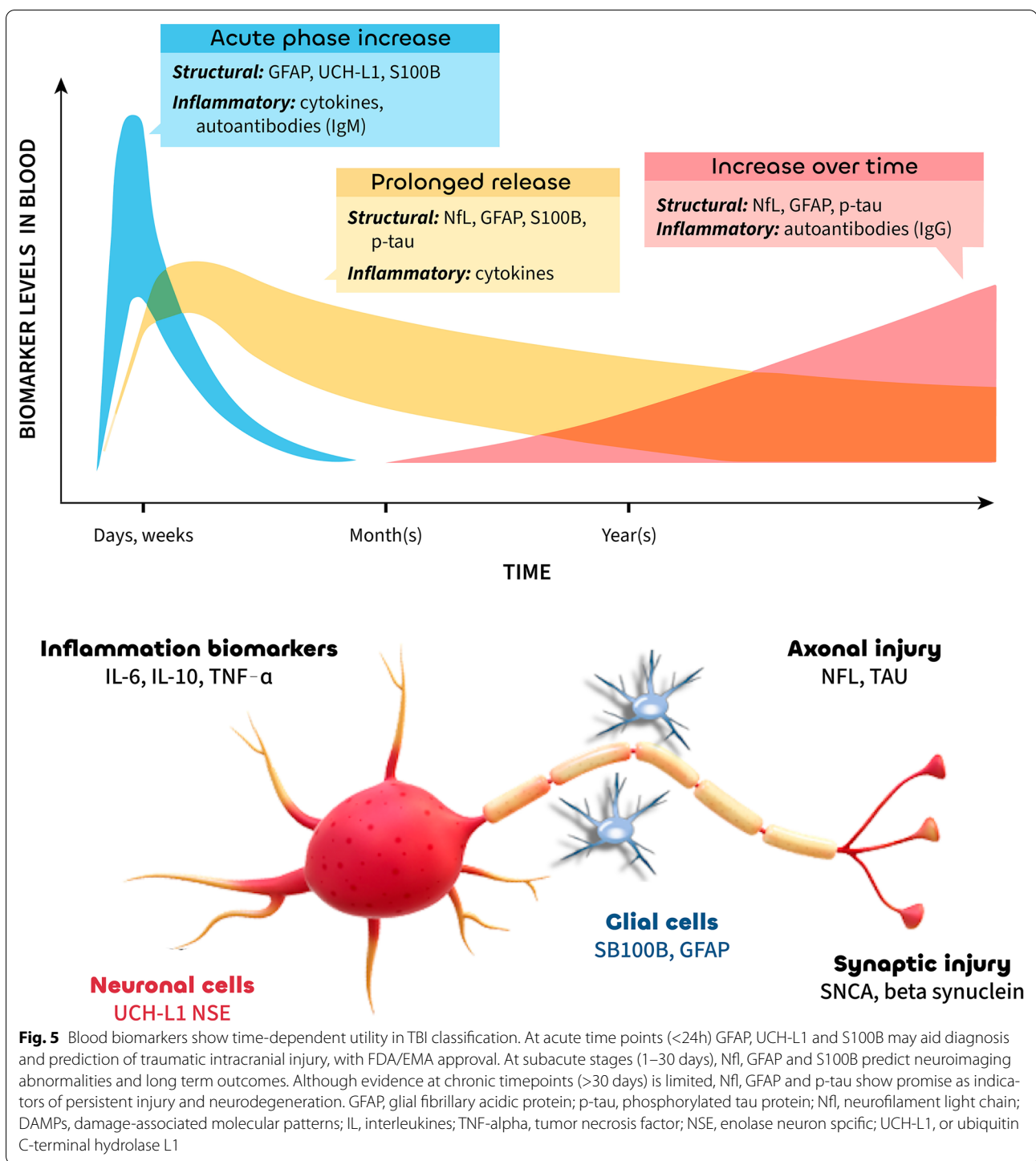
Even for significant injuries, it is expected that the enhancement of traditional rehabilitation approaches with neuroplasticity-targeting therapies and brain-computer interfaces will produce improved long-term functional recovery [125].

Finally, global disparities in TBI care now exist, and addressing these inequalities through telemedicine, standardized guidelines, and capacity-building in low-resource settings is essential, as most TBI now occurs in low- and middle-income countries [2].

The need for large-scale, multicenter trials assessing innovative pharmacologic and non-pharmacologic interventions remains, even while we need to rethink the design of our trials in terms of clarity, efficiency, integration, and alignment with stakeholders [126]. Further research is warranted to better understand the multifactorial factors involved in TBI toward a better understanding of patients’ profiles and phenotypes, treatment individualization, and improvement in patients’ outcomes.

Conclusions

Traumatic brain injury remains an important challenge for clinicians. Aggressive treatment and advances in monitoring have improved mortality and neurological recovery, by focusing on the early detection



and treatment of secondary brain injury that can result from intra or extracranial complications. Questions still remain regarding the best practice and standard of care in these patients and, in particular, on prognostic tools which can potentially help in individualising treatment and defining phenotypes for treatment. Future research

should focus on understanding the natural history of recovery after TBI, the definition of precise criteria and terminology for classifying TBI, gaining a greater understanding of the factors that affect outcomes after TBI to allow precision diagnosis, prognosis, and monitoring in this population.

Supplementary Information

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Declarations

Conflicts of interest

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